IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Brenda F. Baker, *et al.***	Confirmation No.: **7033**
Serial No.: **10/701,265**	Group Art Unit: 1635
Filing Date: **November 4, 2003**	Examiner: **Jennifer Sue Pitrak McDonald**

For: **Chimeric Oligomeric Compounds And Their Use In Gene Modulation**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

APPELLANT'S REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

Appellants submit this Reply in response to the Examiner's Answer dated May 31, 2012 in connection with the above-identified application. This reply is being filed within two months of said answer.

The Examiner Misconstrues The Teachings Of Shibahara

The examiner asserts that "[a]ppellant appears to interpret the rejection has being based primarily on the Wyatt reference" while "Wyatt is relied upon, among other references, to demonstrate the state of the art at the time of the instant rejection."[1] Applicants note that regardless of how the examiner combines the art recited in the rejection, the examiner still has the burden to provide a teaching or suggestion of each claim limitation and a sufficient motivation to assemble the elements of the claim as the applicant has presented in the claims.[2]

[1] Examiner's Answer at pages 9-10.
[2] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007).

The assembly of teachings from the cited references must be made in view of the state of art at the time of the invention and must not rely on applicant's blue print.[3]

In our Appeal Brief, we have discussed each cited reference individually and as a group. As detailed in the Appeal Brief, nothing in the Wyatt article or the remaining cited references would have provided a reason to introduce sugar-modified nucleosides into both strands of an oligonucleotide duplex. The examiner, however, cites the Shibahara application in support of modification of both strands of a duplex[4] even though there is no teaching or suggestion of such a modification. The Shibahara application describes single-stranded antisense ribooligonucleotides targeted against HIV genomic RNA or against HIV DNA integrated into a chromosome. The Shibahara application further describes experiments in which such single-stranded antisense ribooligonucleotides were introduced into cells that had been infected with HIV, and the cytopathic inhibitory effect of the ribooligonucleotides was determined. Although the Shibahara application describes chemical modification of the antisense ribooligonucleotides, including 2'-OCH_3 modifications, the Shibahara application does not describe or suggest any reason to introduce chemical modifications into oligonucleotide duplexes.

Despite the limitations of the teachings of the Shibahara application discussed above, the examiner asserts that the skilled artisan would be motivated to produce an artificially labeled RNA substrate to assist in mechanistic studies based on the alleged teachings of the Shibahara application.[5] Applicants note that in discussion of why the Shibahara application would motivate the skilled artisan to undertake the proposed mechanistic study, no citations are made to specific passages within the Shibahara application.[6] The examiner's construction, which attempts to connect applicant's claims to the teachings of the Shibahara application, appears to be motivated by applicant's teachings rather than a construction motivated by the teachings of the Shibahara application without influence of applicant's blueprint. There is simply no teaching or suggestion in the Shibahara application to modify an oligonucleotide duplex. Indeed, such a study is not consistent with the teachings of the Shibahara application. The objective of the Shibahara application was to develop oligoribonucleotide derivatives which inhibit infection and

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[3] *Id.* and *In re Finch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).
[4] Examiner's Answer at pages 12-13.
[5] *Id.*
[6] *Id.*

proliferation of the AIDS virus.[7] These oligoribonucleotide derivatives were single stranded compounds[8] which were contacted with an isolated RNA strain.[9] The Shibahara application teaches that "anti-AIDS viral activity can be determined by the method described in a publication (cf., Harada, S., et al., Science, 229, 563-566, 1985), using HTLV-1110 (cf., Popovic, M., et al., Science, 224, 497-500, 1984) which is an isolated strain of AIDS virus."[10] Thus, no additional study was necessary to accomplish the objectives of the Shibahara application. As evidenced by these teaching and the specification as a whole, the Shibahara application was directed to finding effective oligoribonucleotide derivatives to combat AIDS not the mechanistic details put forth in the examiner's proposed motivation. Based on the foregoing, the examiner's proposed motivation is insufficient and the rejection should be overturned.

Even if one skilled in the art were motivated to perform a mechanistic study based on the teaching of the Shibahara application (a point applicants do not concede), the examiner's proposed motivation is still insufficient to render the pending claims obvious. In this regard, applicants believe that the examiner relies on the disclosure within the Shibahara application that states "[i]t is noted that all these derivatives show a potent anti-AIDS viral activity, although mechanism on the activity has not been experimentally proven in detail."[11] Even if this were motivation to carry out a mechanistic study, there is simply no reason as to why the study constructed by the skilled artisan would necessarily be the study constructed by the examiner. Many tools are available and the tools which involve oligoribnucleotide modifications involve numerous options for such modifications. The examiner's logic detailing the alleged motivation on pages 12-13 of the Examiner's Answer involves many assumptions and choices, and strays far from the teachings of the Shibahara application. Thus, the examiner's proposed motivation is insufficient and the rejection should be overturned.

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[7] The Shibahara application at page 3, lines 31-34.
[8] *See* the Shibahara application as a whole and page 3, line 35 to page 4, line 57, for example.
[9] The Shibahara application at page 18, lines 11-23.
[10] The Shibahara application at page 18, lines 11-13.
[11] The Shibahara application at page 15, lines 15-16.

The Examiner Errs By Ignoring Record Evidence Of Non-Obviousness

In his discussion of the Declaration of David Corey, the examiner notes that "Baracchini is not currently cited."[12] While this is correct, the declaration must be considered in the context of the prolonged prosecution of the patent and the largely duplicative nature of the pending rejections versus those addressed in the declaration. When the declaration was presented to the Office, the examiner characterized it as non-persuasive. Hoping at long last to resolve this prosecution deadlock, applicants appealed to the Board of Patent Appeals and Interferences and submitted a request for a pre-appeal brief conference that set forth in detail why the claimed oligomeric compounds would not have been obvious at the time of the invention. After the notice of appeal and request for a pre-appeal brief conference were filed, rather than allowing the claims, or even allowing the application to proceed to appeal to finally resolve the outstanding issues, the examiner instead re-opened prosecution, with allegedly "new" grounds for once again rejecting the claims as obvious. The present rejections rely on the Manche article already addressed by appellants and discussed by Dr. Corey. This reference is now combined with new, largely duplicative references, not previously cited throughout the long prosecution history of this application. As explained in our Appeal Brief, these "new" rejections fail for the same fundamental reason as the previous obviousness rejections: the examiner has still not provided a reason why one of skill in the art would have made the claimed compounds prior to invention by the applicants.

In regard to the Manche reference, it offers no reason to make chemically modified oligonucleotides because the duplexes of the Manche reference were synthesized enzymatically, not through chemical synthesis and do not contain any chemical modifications.[13] Further, the Manche article would not have prompted one to make compounds as those presently claimed and indeed, such compounds would have been unsuitable for use in the research described in the Manche article.[14] Such an analysis by an expert in the field is relevant and speaks to the strength of a rejection relying on this reference. As noted above, the remaining references discussed by Dr. Corey are largely duplicative of the teachings of the references cited in the most recent

[12] Examiner's Answer at page 13.
[13] The Corey Declaration at paragraph 18.
[14] The Corey Declaration at paragraph 19.

rejection. As such, Dr. Corey's Declaration does speak to the inventive nature of the instant claims versus the state of the art at the time of the invention.

Conclusion

As explained in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) (citations omitted), "[a]fter evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." It is believed that when the Board considers the present record in this light that the only reasonable conclusion is that the preponderance of evidence weighs in appellants favor. Accordingly, it is respectfully requested that, for the reasons set forth above and in the Appeal Brief, the Board reverse all of the pending obviousness rejections.

Respectfully submitted,

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